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Epidemiology, clinical characteristics, and risk factors for mortality of early- and late-onset invasive candidiasis in intensive care units in China

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Abstract

To identify the epidemiology, treatments, outcomes, and risk factors for patients with early- or late-onset invasive candidiasis (EOIC or LOIC) in intensive care units in China.

Patients were classified as EOIC (≤10 days) or LOIC (>10 days) according to the time from hospital admission to IC onset to identify distinct clinical characteristics.

There were 105 EOIC cases and 201 LOIC cases in this study. EOIC was related to more severe clinical conditions at ICU admission or prior to IC. Significantly, more cases of *Candida parapsilosis* infection were found in patients with LOIC than in those with EOIC. The mortality of EOIC was significantly lower than that for LOIC. Sequential Organ Failure Assessment (SOFA) score at ICI diagnosis in the EOIC group and the interval from ICU admission to ICI occurrence in the LOIC group were identified as risk factors for mortality. Susceptibility to the first-line agent was associated with a lower risk of mortality in the LOIC group.

The mortality rate was significantly lower in the EOIC group, and there were more cases of non-albicans infection in the LOIC group. Susceptibility to the first-line agent was an important predictor of mortality in the LOIC group. SOFA score at ICI diagnosis in the EOIC group and interval from ICU admission to ICI occurrence in the LOIC group were identified as risk factors for mortality.

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, CLSI = Clinical Laboratory Standards Institute, CNS = central nervous system, COPD = chronic obstructive pulmonary disease, EOIC = early-onset IC, HCA = healthcare-associated *Candidemia*, IC = invasive candidiasis, ICI = invasive candidiasis infection, ICUs = intensive care units, LOIC = late-onset IC, SD = standard deviation, SOFA = Sequential Organ Failure Assessment.

Keywords: early-onset invasive candidiasis, epidemiology, intensive care unit, late-onset invasive candidiasis, risk factors

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1. Introduction

The incidence of invasive candidiasis (IC), the third most common cause of infection in intensive care units (ICUs) worldwide, accounts for 17% of infections[1] and has been increasing throughout the world in recent years. Due to the high associated mortality and hospital costs,[2,3] IC is an increasing concern, especially for critically ill patients. *Candida albicans* have been the most commonly isolated strain in hospital patients for the past 20 years; however, the epidemiological trend of IC has changed towards increasing rates of infection with non-albicans strains in recent years.[4] Particularly, *Candida glabrata* is now responsible for 15% to 20% of Candida infections in most countries, and the susceptibility of Candida to the azole antifungals is reduced.[5,6]

Knowledge of IC epidemiology, including geographical differences, is an important guide to prescribing practices and health policy and has far reaching clinical implications.[7] In addition, the epidemiology of IC varies with the time of onset,[7,8] and candidaemia occurring more than 48 hours after admission is usually described as being healthcare-associated candidaemia (HCA).[9–11] There are few studies on the clinical characteristics and outcomes of early-onset IC (EOIC) with variable time definitions, ranging from 2 to 14 days after hospital admission.[12–14] In a cohort of critically ill patients with candidaemia, onset within 14 days of hospital admission, higher mortality, and hospital costs were closely associated with inadequate initial antifungal therapy.[13] To date, there has been no scientific agreement on the definitions of EOIC and LOIC.

Various times for EOIC definition in a few studies on the clinical characteristics and outcomes of EOIC have ranged from 2 to 14 days after hospital admission, with 1 study comparing the clinical characteristics with prognosis of candidaemia within or 10 days after admission,[14] whereas most studies identified EOIC as IC onset within 48 hours of hospital admission.[12,15,16]

Because no clinical data for EOIC or LOIC in patients in Chinese ICUs have been reported so far, and the development of IC caused by opportunistic pathogens may be slow, we conducted an observational, multicentre study in 67 ICUs in China between November 2009 and April 2011[17] and compared the epidemiology, clinical characteristics, treatment, and risk factors in patients with EOIC (≤10 days) and LOIC (>10 days) after hospital admission in Chinese ICUs.

2. Methods

2.1. Study design and patients

The patients were from the China-SCAN study conducted from November 2009 to April 2011.[17] In brief, 67 closed ICUs in general hospitals distributed throughout China participated in the observational multicentre study of proven IC. Patient inclusion criteria were age ≥18 years with clinical signs of infection and at least 1 of the following diagnostic criteria: histopathological, cytopathological, or direct microscopic confirmation of yeast cells in a specimen obtained by needle aspiration or biopsy from a normally sterile site; at least 1 peripheral blood culture positive for *Candida*; or positive *Candida* culture from a sample obtained by sterile technique from a normally sterile site. Samples from a drain, including urine and respiratory tract secretions that were not confirmed to be sterile were excluded. Patients were grouped according to the time of onset of the disease after hospital admission: ≤10 days for EOIC or >10 days for LOIC. APACHE II[18] and Sequential Organ Failure Assessment (SOFA)[19] scores were used to evaluate disease severity at the time of patient ICU admission and IC diagnosis. The time of onset refers to the date of diagnosis of IC, which was defined as the date when the first positive specimen was obtained. Chronic hepatic insufficiency was defined as biopsy-proven cirrhosis and portal hypertension, episodes of past upper gastrointestinal bleeding attributed to portal hypertension, or prior episodes of hepatic failure/encephalopathy/coma. Gastrointestinal dysfunction was defined as hemorrhage, food intolerance, perforation, surgery, acalculouschole cystitis, or intra-abdominal hypertension. Severe sepsis referred to the presence of known or suspected infection in association with systemic inflammatory response syndrome and organ dysfunction. Septic shock was defined as sepsis-induced hypotension that persisted despite adequate fluid resuscitation. Isolated *Candida* species were cultured and identified in vitro thereafter tested against amphotericin B, fluconazole, voriconazole, itraconazole, and caspofungin according to the CLSI M27-A3 microbroth dilution method[20] at the Research Center for Medical Mycology, Peking University First Hospital, Beijing, China. The sensitivity cut-offs values were ≤8 mg/L for fluconazole, ≤1 mg/L for voriconazole, ≤2 mg/L for caspofungin, ≤0.125 mg/L for itraconazole, and ≤2 mg/L for amphotericin B. The epidemiologic data, pathogen-related, clinical characteristics, and therapeutic data were collected from all eligible patients treated in the participating ICUs. The study was approved by the Ethics Committee of Zhongda Hospital of Southeast University, the lead investigation site.

2.2. Statistical analysis

Continuous variables were described as mean ± standard deviation (SD) or median and range and compared with Student *t* tests if normally distributed or by Wilcoxon tests if non-normally distributed. Categorical variables were described as frequencies and percentages and compared with chi-squared tests or Fisher exact tests. Multivariate analysis with Cox proportional hazard model was used to identify independent risk factors for mortality among all variables with a P value <.05 on chi-squared test. P values <.05 were considered as statistically significant. All statistical analyses were performed using SAS 9.1 (SAS Institute INC, Cary NC).

3. Results

3.1. Patient characteristics

Three hundred sixty-six patients were diagnosed with IC among a total of 96,060 ICU patients from 67 centers throughout China were included in this study. Out of the 306 patients, 290 (94.8%) were diagnosed solely based on at least 1 positive blood culture; 12 (3.9%) cases were diagnosed based on positive fluid culture from a normally sterile site (3 cases of CNS candidiasis, 8 cases of intra-abdominal candidiasis, and 1 case of candida pleuritis); and 3 were diagnosed based on candidaemia and positive culture from a normally sterile site. One pulmonary candidiasis was confirmed by histopathology.

Of these 306 patients, 105 cases were classified as EOIC and 201 cases as LOIC. The median (Q1, Q3) times between ICU admission and confirmed diagnosis of IC were 4 days (Q1–Q3, 1–7 days) and 17 days (Q1–Q3, 10–33 days) in the EOIC and LOIC groups, respectively. The main characteristics of the patients are detailed in Table 1.

The mean (SD) SOFA scores at diagnosis were 11.7 (±3.8) and 10.2 (±3.3; P < .001) in the EOIC and LOIC groups, respectively. The most common underlying diseases in the 2 groups were type 2 diabetes, chronic cardiac dysfunction, chronic obstructive pulmonary disease (COPD), and solid tumors. There were more patients with solid tumors in the LOIC group (P = .001) than in the EOIC group. Compared with patients in the LOIC group, more patients were treated with surgery in the EOIC group (46.7% vs 33.8%, P = .035). Other risk factors present in 40% to 60% of patients during the 2 weeks prior to study entry were gastrointestinal dysfunction and total parenteral nutrition in the 2 groups. More than 50% of patients in the EOIC and LOIC groups (59.0% vs 89.1%, P < .001) had a recent history of antibiotic therapy, and more than 70% of patients (76.2% vs 77.6%, P = .659) had invasive mechanical ventilation and central venous catheterization (76.2% vs 86.1%, P = .03; Table 1).

3.2. Microbiology data

Although the IC diagnosis was confirmed for all 306 patients in local laboratories, not all hospitals sent isolates to the central laboratory for confirmation (reasons included individual hospital policy and suboptimal storage or handling of isolates). Thus, the dataset was incomplete in this regard. A total of 387 isolates from 244 patients, 86 patients in the EOIC group, and 158 patients in the LOIC group were analyzed. *C albicans* was the most prevalent species in both EOIC and LOIC cases (47.7% and 36.1%, P = .101 in the EOIC group and LOIC group, respectively), while the proportion of different non-*C albicans* infections tended to be different between patients with EOIC and LOIC. Especially for *Candida tropicalis* and *Candida parapsilosis* infections, *C parapsilosis* was more prevalent

Table 1

Baseline characteristics and risk factors of 306 patients diagnosed with IC according to the time at risk.

Category	EOIC (n = 105)	LOIC (n = 201)	P
Interval between hospital admission and ICI diagnosis (d), median (Q1, Q3)	4 (2.7)	26 (16, 50)	<.001
Interval between ICU admission and ICI diagnosis, median (Q1, Q3)	4 (1.7)	17 (10, 33)	<.001
Age (y), mean (SD)	56.9 (19.94)	64.0 (19.67)	.003
Gender, male/female	68/37	142/59	.302
Concomitant disease, n (%)			
Solid tumor	9 (8.6)	48 (23.9)	.001
Haematological malignancy	1 (1.0)	2 (1.0)	1.00
Diabetes	18 (17.2)	50 (24.9)	.122
Chronic obstructive pulmonary disease	10 (9.5)	25 (12.4)	.571
Chronic renal insufficiency	11 (10.5)	22 (11.0)	.900
Chronic hepatic insufficiency	2 (1.9)	14 (7.0)	.063
Chronic cardiac dysfunction	16 (15.2)	48 (23.9)	.078
Severe sepsisat ICI diagnosis, n (%)	63 (60.0)	104 (51.7)	.185
Septic shock at ICI diagnosis, n (%)	42 (40.0)	44 (21.9)	.001
Illness severity at ICU admission, mean (SD)			
APACHE II score	28.2 (6.4)	26.7 (7.6)	.105
SOFA score	12.1 (3.6)	10.6 (3.2)	<.001
Illness severity at ICI diagnosis, mean (SD)			
APACHE II score	27.6 (7.1)	26.8 (7.0)	.355
SOFA score	11.7 (3.8)	10.2 (3.3)	<.001
Immune compromised	5 (4.8)	12 (6.0)	.796
Immunosuppressant therapy*	4 (3.9)	11 (5.5)	.552
HIV infection	1 (1.1)	1 (0.5)	1.000
Neutropenia	2 (1.9)	3 (1.5)	1.000
Gastrointestinal dysfunction	59 (56.2)	122 (60.7)	.502
Total parenteral nutrition	44 (41.9)	86 (42.8)	.882
Surgery	49 (46.7)	68 (33.8)	.035
Abdominal	40 (38.1)	48 (23.9)	.010
Time from surgery to IC (d), median (min, max)	8 (1, 20)	10.5 (0, 51)	.012
Antibiotic used before IC diagnosis	62 (59.0)	179 (89.1)	<.001
Invasive mechanical ventilation	80 (76.2)	156 (77.6)	.659
Catheterization			
Central venous	80 (76.2)	173 (86.1)	.030
Drainage tube	36 (34.3)	75 (37.3)	.601
Urethral	80 (76.2)	152 (75.6)	.912

APACHE II = Acute Physiology and Chronic Health Evaluation II, EOIC = early-onset IC, IC = invasive candidiasis, ICI = invasive candidiasis infection, ICUs = intensive care units, LOIC = late-onset IC, SD = standard deviation, SOFA = Sequential Organ Failure Assessment.

* Steroid therapy: 0.5 mg/kg/d of prednisone over 1 month (n = 8), cancer chemotherapy (n = 7), post-solid organ transplant immunosuppression (n = 2), allogeneic bone marrow or allogeneic haematopoietic stem cell transplantation (n = 1), or tumor necrosis factor therapy (n = 3).

in LOIC cases than in EOIC cases (10/86, 11.6% vs 45/158, 28.5%, $P = .002$), whereas *C tropicalis* was more common in EOIC cases (20/86, 23.3% vs 21/158, 13.3%, $P = .05$). There were no statistical differences among the distributions of other species within the 2 groups (Table 2).

Table 2

Species distribution in 244 patients with EOIC or LOIC.

Fungal species	EOIC (n = 86)	LOIC (n = 158)	P
Candida albicans	41 (47.7%)	57 (36.1%)	.101
Candida tropicalis	20 (23.3%)	21 (13.3%)	.05
Candida parapsilosis	10 (11.6%)	45 (28.5%)	.002
Candida glabrata	11 (12.8%)	16 (10.1%)	.529
Candida guilliermondii	0	4 (2.5%)	.300
Candida haemulonii	0	4 (2.5%)	.300
Candida krusei	1 (1.2%)	0	.353
Other rare species*	1 (1.2%)	6 (3.8%)	.239
Mixed infections	2 (2.3%)	5 (3.2%)	1.00

EOIC = early-onset IC, LOIC = late-onset IC.

* Other rare species included: *Lodderomyces elongisporus*, *Candida ernobii*, *Candida pelliculosa*, *Candida lipolytica*, *Candida norvegensis*.

3.3. Treatment and outcomes

The overall mortality rate of all the patients was 36.6% (112/306), and the mortality in the EOIC group was significantly lower than that in the LOIC group (30/105, 28.6% vs 82/201, 40.8%, $P = .045$). A total of 268/306 (87.6%) patients (89 in the EOIC group and 179 in the LOIC group), received antifungal therapy. The most commonly used antifungal agent was fluconazole, followed by the echinocandins. There was no significant difference between the EOIC and LOIC groups in the first-line antifungal agents used or in the susceptibility to the first-line agent (Table 3).

3.4. Risk factors associated with EOIC mortality

The results of univariate analysis of the factors associated with mortality among 105 patients with EOIC (30 nonsurvivors and 75 survivors) are presented in Table 4: patients with a higher SOFA score at IC diagnosis, severe sepsis, invasive mechanical ventilation, or gastrointestinal dysfunction had a higher mortality. However, multivariate analysis by COX model showed that only SOFA at ICI diagnosis tended to be associated with decreased survival (hazard ratio = 1.09, $P = .0543$; Table 5).

Table 3

Treatments and outcomes of 306 patients with EOIC or LOIC.

Category	EOIC (n = 105)	LOIC (n = 201)	*P*
Initial antifungal agent*			
Amphotericin B	3 (3.4%)	3 (1.7%)	.843
Fluconazole	35 (39.3%)	66 (36.9%)	.930
Voriconazole	17 (19.1%)	32 (17.9%)	.951
Itraconazole	5 (5.6%)	17 (9.5%)	.351
Caspofungin	19 (21.3%)	45 (25.1%)	.466
Micafungin	9 (10.1%)	14 (7.8%)	.651
Combined therapy	1 (1.1%)	2 (1.1%)	.997
Untreated	16 (15.2%)	22 (10.9%)	.280
Susceptibility to first-line antifungals	55 (85.9%)	102 (80.3%)	.338
Outcome			
Death/survival	30/75	82/119	.045

EOIC = early-onset IC, LOIC = late-onset IC.

* The calculated proportion of patients who received antifungal therapy (89 patients in EOIC group and 179 patients in LOIC group).

3.5. Risk factors associated with LOIC mortality

The results of univariate analysis for 201 patients with LOIC (82 nonsurvivors and 119 survivors) are presented in Table 6. Older patients and patients with severe sepsis, chronic renal insufficiency, and higher SOFA score had a higher risk of mortality. Susceptibility to the first-line agent was associated with a lower risk of mortality. Multivariate analysis by the Cox model showed that interval from ICU admission to ICI occurrence was a risk factor for mortality (hazard ratio = 1.009, $P = .001$; Table 7).

4. Discussion

Investigations of IC according to the time of onset after hospital admission are rare. To our best knowledge, this is the first study of the epidemiology, treatment, outcomes, and risk factors for mortality in EOIC and LOIC patients in Chinese ICUs in which IC was diagnosed by the same strict criteria used in another study.[21] In this study, we found that SOFA scores were higher at either ICU admission or IC diagnosis, and more cases of septic shock at IC diagnosis occurred in patients with EOIC than in those with LOIC, suggesting that the clinical conditions of patients with EOIC are more severe than those with LOIC both at ICU admission and at IC diagnosis.

C albicans was found to be the most prevalent Candida species in patients with both EOIC and LOIC; however, non-albicans species constituted 63.9% of isolates in patients with LOIC and 52.3% of isolates in patients with EOIC. These distributions of *C albicans* and non-albicans species were in accordance with those in recent reports both in China and other countries.[20–22] The reasons for the gradually increasing incidence of non-alibicans infections may be ascribed to the increased use of relatively low-cost azoles, an ageing population, the clinical condition of patients, and central venous catheter placement. The proportions of different non-albican species were different between patients

Table 4

Differences between EOIC patients (n = 105) who experienced death or survival.

	Univariate analysis		
Variable	Death (n = 30)	Survival (n = 75)	*P*
Interval between ICU admission and ICI diagnosis, median (Q1–Q3)	4.5 (3, 7)	4 (2, 7)	.288
Age (y), median (range)	64 (21~83)	57 (20~85)	.556
Gender (male)	21 (70.0%)	47 (62.7%)	.508
Severe sepsis	23 (76.7%)	40 (53.3%)	.030
Septic shock	17 (56.7%)	25 (33.3%)	.046
Invasive mechanical ventilation	28 (93.3%)	52 (69.3%)	.009
Concomitant disease, n (%)			
Solid tumor	3 (10.0%)	7 (8.0%)	.741
Haematological malignancy	–	2 (1.3%)	1.000
Diabetes	5 (16.7%)	13 (17.3%)	.935
Chronic obstructive pulmonary disease	3 (10.0%)	7 (9.3%)	1.000
Chronic renal insufficiency	3 (10.0%)	8 (10.6%)	1.000
Chronic hepatic insufficiency	–	2 (2.7%)	1.000
Chronic cardiac dysfunction	6 (20.0%)	10 (13.3%)	.348
Gastrointestinal dysfunction	22 (73.3%)	37 (49.3%)	.030
Illness severity at ICU admission			
APACHE II score, mean (SD)	29.0 (6.14)	28.0 (6.48)	.494
SOFA score, mean (SD)	13.7 (2.40)	11.4 (3.81)	.001
Illness severity at ICI diagnosis			
APACHE II score, mean (SD)	28.3 (7.89)	27.3 (6.74)	.588
SOFA score, mean (SD)	13.1 (3.07)	11.2 (3.89)	.024
Fungal species*			
Candida albicans	10 (47.6%)	31 (47.7%)	1.000
Non-*Candida albicans*	11 (52.4%)	34 (52.3%)	
Candida tropicalis	8 (38.1%)	12 (18.5%)	.079
Candida parapsilosis	2 (9.5%)	8 (12.3%)	1.000
Candida glabrata	1 (4.8%)	10 (15.4%)	.281
Antifungal treatment	25	64	
First-line antifungal agent for at least 48 h	14	51	
Azoles	10 (71.4%)	30 (58.8%)	.722
Echinocandins	4 (28.6%)	19 (37.3%)	
Others	–	2 (3.9%)	
Susceptibility to first-line antifungals†	15 (83.3%)	40 (87.0%)	.703

APACHE II = Acute Physiology and Chronic Health Evaluation II, EOIC = early-onset IC, ICI = invasive candidiasis infection, ICUs = intensive care units, SD = standard deviation, SOFA = Sequential Organ Failure Assessment.

* The proportions of fungal species were calculated using stains identified by the central lab (21 cases in death group and 65 patients in survival group).

† The calculated proportion of patients who received antifungal therapy and identified species (18 patients in death group and 46 patients in survival group).

Table 5

Results of Cox model analysis for risk factors associated with mortality among EOIC patients (n = 105).

Variables	Hazard ratio	Coefficient	Standard error	Chi-squared	*P*
Chronic cardiac dysfunction	1.85	0.615	0.392	2.454	.117
Invasive mechanical ventilation	2.03	0.709	0.515	1.894	.169
Age	1.00	0.003	0.009	0.108	.743
Severe sepsis	1.25	0.219	0.382	0.331	.565
SOFA score at ICU admission	1.02	0.019	0.024	0.638	.424
SOFA score at ICI diagnosis	1.09	0.090	0.047	3.703	.054

Survival time is from ICI onset to discharge or death. EOIC = early-onset IC, ICI = invasive candidiasis infection, ICUs = intensive care units, SOFA = Sequential Organ Failure Assessment.

Table 6

Differences between LOIC patients (n = 201) who experienced death or survival.

Variable	Univariate analysis		
	Death (n = 82)	Survival (n = 119)	P
Interval between ICU admission and ICI diagnosis, median (Q1–Q3)	20.5 (11–55)	14 (9–27)	.008
Age (y), median (range)	77.5 (19–96)	62 (18–93)	.002
Gender (male)	59 (72.0%)	83 (69.7%)	.755
Severe sepsis	51 (62.2%)	53 (44.5%)	.015
Septic shock	24 (29.3%)	20 (16.8%)	.039
Invasive mechanical ventilation	69 (84.1%)	87 (73.1%)	.065
Concomitant disease, n (%)			
Solid tumor	25 (30.5%)	23 (19.3%)	.068
Haematological malignancy	1 (1.2%)	–	.651
Diabetes	26 (31.7%)	24 (20.2%)	.070
Chronic obstructive pulmonary disease	11 (13.4%)	14 (11.8%)	.829
Chronic renal insufficiency	14 (17.0%)	8 (6.8%)	.021
Chronic hepatic insufficiency	7 (8.5%)	7 (5.9%)	.575
Chronic cardiac dysfunction	23 (28.0%)	25 (21.0%)	.249
Illness severity at ICU admission			
APACHE II score, mean (SD)	28.0 (7.22)	25.8 (7.68)	.081
SOFA score, mean (SD)	10.8 (2.96)	10.4 (3.38)	.500
Illness severity at ICI diagnosis			
APACHE II score, mean (SD)	27.5 (6.67)	26.24 (7.27)	.248
SOFA score, mean (SD)	11.1 (3.05)	9.6 (3.29)	.001
Fungal species*			
Candida albicans	19 (29.7%)	38 (40.4%)	.181
Non-*Candida albicans*	45 (70.3%)	56 (59.6%)	
Candida tropicalis	7 (10.9%)	14 (14.9%)	.634
Candida parapsilosis	21 (32.8%)	24 (25.5%)	.371
Candida glabrata	10 (15.6%)	6 (6.4%)	.066
Antifungal treatment	71	108	
First-line antifungal agent for at least 48 h	64	88	
Azoles	43 (67.2%)	54 (61.4%)	.750
Echinocandins	20 (31.3%)	33 (37.5%)	
Others	1 (1.6%)	1 (1.1%)	
Susceptibility to first-line antifungals†	35 (70.0%)	67 (87.0%)	.023

APACHE II = Acute Physiology and Chronic Health Evaluation II, ICI = invasive candidiasis infection, ICUs = intensive care units, LOIC = late-onset IC, SD = standard deviation, SOFA = Sequential Organ Failure Assessment.

* The proportions of fungal species were calculated using stains identified by the central lab (64 cases in death group and 94 patients in survival group).

† The calculated proportion of patients who received antifungal therapy and identified species (50 patients in death group and 77 patients in survival group).

with EOIC and LOIC. The reason *C tropicalis* was the most prevalent non-albicans species in EOIC may be that there were severe complications associated with hospitalization, more surgeries, and higher SOFA scores in this group, whereas the most common non-albicans isolate in LOIC was *C parapsilosis*, which may be caused by the longer duration of admission and intravenous catheter indwelling.

The crude mortality rate in the EOIC group was significantly lower than that in the LOIC group. This is in line with previous findings from a study in which mortality was significantly lower in patients with EOIC (≤10 days after admission) compared with patients with candidaemia diagnosed 10 days after admission.[14] The explanation for this lower mortality in the EOIC group is likely related to less severe infection. However, the EOIC group had higher SOFA scores, at ICI, which showed a contradictory result. Furthermore, Cox hazard ratio analysis showed only SOFA score at ICI diagnosis in the EOIC group was a risk factor for mortality. The reason could be that despite the severity in the EOIC group, these patients were younger and had used less antibiotics previously. Finally, the interval from ICU admission to ICI occurrence was identified as a risk factor for mortality in the LOIC group, which was logical given that a prolonged ICU stay itself is often related to poor outcomes.

We found that the most commonly used antifungal drug was fluconazole followed by the echinocandinsin both the EOIC and LOIC groups. Based on the previous China-SCAN study, the resistance to itraconazole is reasonably high, and the sensitivity to fluconazole is relatively low among non-albicans species[23]; similarly, resistance to fluconazole is widespread, especially among *C glabrata* and *C parapsilosis* infections in another study.[22] Therefore, it is important to monitor the susceptibility and earlier use of effective non-azole antifungals in patients with probable or proven azole resistance, and an early and effective treatment of IC is critical for improved prognosis.

At least 3 limitations exist in the present study. First, not all isolates were sent to the central laboratory for our study population, so that the distribution of *Candida* species between EOIC and LOIC might not be precisely represented by our evaluation; second, differences in clinical practices across centers might influence the diagnosis and management of IC, and thus, the mortalities in the 2 different groups might not be precise. The average number of patients included from each center was 4.6 patients/center, and a mixed model might need a larger sample size. Third, the pathogenesis of IC most likely reflects a multistep process in which comorbidities, host factors, and colonization contribute to the invasion of the Candida spp.[24] Thus, a further study with a larger sample size is needed to confirm the findings of our present study.

Nevertheless, significant differences were observed between patients with LOIC and EOIC in terms of mortality rates and non-albican *Candidia* species infection. SOFA score at ICI

Table 7

The results of Cox model analysis for risk factors associated with mortality in LOIC (n = 201).

Variables	Hazard ratio	Coefficient	Standard error	Chi-squared	P
Solid tumour	2.04	0.712	0.443	2.582	.108
Diabetes	1.42	0.353	0.364	0.943	.332
Chronic hepatic insufficiency	1.25	0.225	0.483	0.217	.641
Invasive mechanical ventilation	1.72	0.544	0.501	1.177	.278
Age	0.99	−0.011	0.010	1.177	.278
APACH II score at ICI diagnosis	1.04	0.035	0.027	1.635	.201
Susceptible to first-line antifungal agents	0.37	−0.985	0.375	6.909	.009
Interval from ICU admission to ICI occurrence	1.01	0.009	0.003	10.823	.001

Survival time is from ICI onset to discharge or death.

APACHE II = Acute Physiology and Chronic Health Evaluation II, ICI = invasive candidiasis infection, ICUs = intensive care units, LOIC = late-onset IC.

diagnosis was associated with higher mortality in EOIC, whereas a longer interval from ICU admission to ICI onset played a more important role for LOIC. Also, susceptibility to the first-line agent was a predictor of mortality in LOIC. Our findings highlight the need for earlier use of effective antifungals to reduce mortality.

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